TREATMENT OF CHORIOCARCINOMA WITH A COMBINATION OF CYTOTOXIC DRUGS

BY

K. D. BAGSHAWE, M.B., M.R.C.P.
Senior Medical Registrar, St. Mary's Hospital, London

AND

JANETTA M. McDONALD, Ph.D., B.Sc.
Senior Biologist, Endocrine Unit, Chelsea Hospital for Women, London

It is known that both normal embryonic development in the rat and growth of the female genital tract are dependent upon the availability of folic acid (Nelson and Evans, 1949; Hertz and Tullner, 1949). It was therefore postulated by Hertz and his colleagues (Li *et al.*, 1956; Hertz *et al.*, 1958) that trophoblastic tumours originating in the foetal chorion might prove sensitive to folic-acid antagonists. These workers introduced the administration of anti-folic-acid therapy to patients with malignant trophoblastic tumours and reported five complete remissions and 17 partial remissions in a series of 27 cases. Resistance to folic-acid antagonists appeared to develop during therapy in some of their patients.

By crude analogy with the antibiotics, it seemed likely that resistance to cytotoxic substances, especially those with an antimetabolite action, would develop less readily when used in combination. There is also some experimental evidence which suggests that combinations of cytotoxic drugs may be more effective than the same drugs used alone (Skipper *et al.*, 1954). Augmented toxic effects on normal tissues would also be expected.

The use of a combination of drugs administered concurrently in the treatment of two cases of pulmonary hypertension due to trophoblastic tumours was described briefly by Bagshawe and Brooks (1959). The present paper describes the results of combined cytotoxic therapy in six patients who had chorionic growths. Clearly the use of such combinations of drugs is largely empirical, and much work will be required to find the best combinations. The drugs chosen in the first stage of this study were the folic-acid antagonist methotrexate (4-amino-N^{10}-methylpteroylglutamic acid), which blocks the conversion of folic to folinic acid, and 6-mercaptopurine. The latter drug has also been shown to exert a severe toxic effect on foetal tissues and acts as an antagonist of hypoxanthine and adenine. It was also decided that, should resistance to this combination of drugs develop, then a drug of the nitrogen-mustard group, such as chlorambucil, would be employed in place of the 6-mercaptopurine.

Methods

Diagnosis was established by histological examination or by the clinical and radiological findings in conjunction with elevated gonadotrophin excretion. The well-known difficulties in the histological diagnosis of choriocarcinoma are not considered here, since all six cases had evidence of multiple metastases.

The urinary gonadotrophin excretion was assayed in terms of the effect upon mouse uterine weight (Klinefelter *et al.*, 1943; Loraine and Brown, 1954). This bioassay is of a semi-quantitative nature, but was adequate for the measurement of the major changes observed in the present series. The values obtained in this laboratory in non-pregnant pre-menopausal women are below 100 mouse units/day, and in post-menopausal or oophorectomized women the values are usually in the range 200–400 mouse units/day.

Recently these results have been supplemented by estimations of human chorionic gonadotrophin in terms of international units, but the results are not included in this communication. A modification of the method of Loraine (1950) was employed, and details of this and other aspects of the biological assays will be published later.

Surgical Treatment.—In the present series of cases hysterectomy and bilateral oophorectomy had been performed on two patients before starting cytotoxic therapy. One patient had hysterectomy and unilateral oophorectomy and one had hysterectomy alone. Two cases had no surgical treatment.

Radiotherapy.—Case 3 had *x*-ray therapy to the eyes before cytotoxic treatment was started.

Drug Treatment.—Methotrexate and 6-mercaptopurine were given concurrently in divided doses for courses of three to five days. The patients received between 4 and 12 such courses. The usual dose of methotrexate was 25 mg. a day in divided doses by mouth, and 6-mercaptopurine was given in doses of 600 mg. daily by the same route. Both doses are grossly in excess of those in common use. A five-day course of treatment was given unless there were residual effects from previous treatment. Antibiotic cover was given during and after each course of treatment, and was continued until the white-cell count had returned to normal. Chlorambucil was given in doses of 10 mg. daily for 6- or 10-day courses, and methotrexate was given during the last three to five days of each course of chlorambucil. The interval between courses was kept as short as was compatible with reasonable safety. The chief limiting factors in this were stomatitis and the peripheral blood picture. The gonadotrophin excretion fell after each course but increased rapidly again if further treatment were delayed, and this rise probably indicated a recurrence of tumour growth. It was sometimes necessary, therefore, to give a further course of therapy even though the total leucocyte count was still depressed. Such courses were usually of only three days' duration, but, even so, they were often followed by severe toxic reactions. It was found essential to base the timing and duration of each course of treatment on frequent, sometimes hourly, assessments of the patient's condition. Such assessments were made difficult by the fact that the toxic effects were maximal several days after completion of each course.

Terminal Phase of Treatment.—Treatment was continued at the maximum intensity which the patient could tolerate until the gonadotrophin titre had been within the normal range for a period of 6 to 10 weeks, and only when this was achieved have we considered the patient to be in a state of hormonal remission.

Case Histories

The clinical features and initial response to treatment in Case 1 were described in a previous paper (Bagshawe and Brooks, 1959), and Case 2 was described in an addendum to the same paper. The main features of all six cases are summarized in Tables I and II.

TABLE I

Case No.	Age	Pelvic Findings	Pulmonary Metastases	Other Metastases	Surgical Treatment	General Condition at Start of Cytotoxic Therapy
1	30	Nil diagnostic	Multiple embolism and pulmonary hypertension	None found	Hysterectomy; unilateral oophorectomy	Gross dyspnoea and anoxaemia
2	28	,, ,,	Severe pulmonary hypertension	,, ,,	Nil	Severe exertional dyspnoea
3	24	7 cm. diameter uterine tumour, choriocarcinoma	Several small metastases on *x*-ray film	Bilateral retinal deposits	Hysterectomy and oophorectomy	Wasted. Severe bilateral impairment of vision
4	24	5 cm. diameter uterine tumour, choriocarcinoma	Multiple metastases	Abdominal glands	,, ,,	Fair
5	23	Mass in right fornix. Curettings—choriocarcinoma	,, ,,	Vagina	Nil	,,
6	31	Malignant mole, 1954	One large, several smaller metastases	Epidural and intracranial	Hysterectomy	Staphylococcal pneumonia. Cauda equina lesion, urinary incontinence, and infection

TABLE II

Case No.	Treatment		Total Dosage			Gonadotrophin Titre M.U.U.		Duration of Remission in Months	Other Features
	No. of Courses	Duration (Months)	Methotrexate (mg.)	6-Mercaptopurine (g.)	Chlorambucil (mg.)	At Onset of Treatment	May, 1960		
1	10	7	1,200	28·8	—	300,000	25	19	Complete remission
2	7	6	725	17·4	—	50,000	75	18	Persistent pulmonary hypertension
3	12	6½	1,250	30·0	—	4,500	150	6	Complete remission. Only slight impairment visual acuity
4	14	9	975	32·2	300	2,000,000	200	2	Marked bone marrow depression during treatment. Complete remission
5	5	5	650	—	—	650,000	25	6	Complete remission. Normal menstruation
6	4		500	11·5	—	?	100	—	Died after 4 courses of treatment. Pyelonephritis. Necrotic cerebral and pulmonary tumours

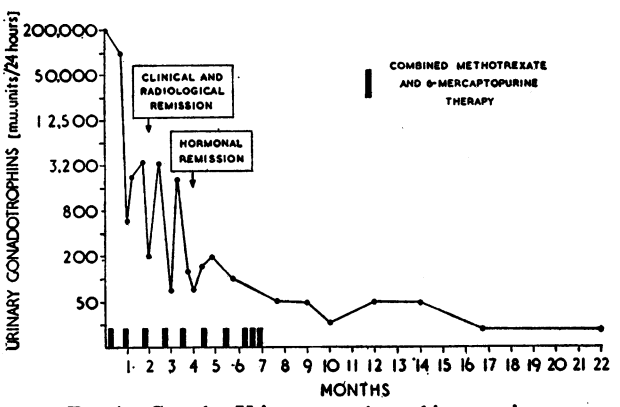


FIG. 1.—Case 1. Urinary gonadotrophin excretion.

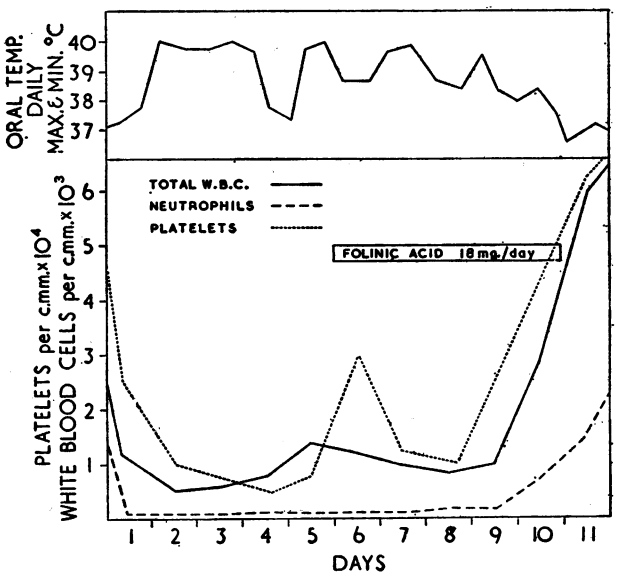


FIG. 2.—Case 1. Leucopenia complicated by staphylococcal infections after tenth treatment.

Case 1 (St. Mary's Hospital).—This patient had recurrent pulmonary embolism leading to severe pulmonary hypertension. Hysterectomy for menorrhagia failed to provide the diagnosis, but this was made subsequently on the basis of raised gonadotrophin excretion. At the time treatment started the patient was severely dyspnoeic at rest. Though severe toxic effects followed the first course of therapy, the improvement in her respiratory function was rapid enough to allow her to leave hospital temporarily only two weeks after the start of treatment. A total of 10 courses of treatment was given during a period of six months (Fig. 1). After the final course of treatment severe leucopenia developed and was complicated by numerous staphylococcal lesions in the skin and lungs. Haematopoietic recovery followed treatment with fresh blood transfusions and folinic acid (Fig. 2). The pulmonary-artery pressure and electrocardiogram have reverted to normal, and complete clinical, radiological, and hormonal remission has persisted since November, 1958. (Time of reporting May, 1960.)

Case 2 (Radcliffe Infirmary and St. Mary's Hospital).—This 28-year-old woman presented with pulmonary hypertension which had first caused symptoms three months after a normal full-term delivery. Diagnosis was established by gonadotrophin assay. Seven courses of treatment were given, and complete hormonal remission has persisted since November, 1958. Marked improvement in exercise tolerance was noted during therapy, and it seemed probable that the pulmonary hypertension had lessened. Cardiac catheterization after completion of therapy showed, however, that, though there had been an appreciable fall in the pulmonary vascular resistance, the pulmonary-artery pressure was grossly unchanged. After discharge from hospital the improved exercise tolerance persisted for four months but then deteriorated. This patient appears to have developed an irreversible pulmonary hypertension.

Case 3 (Mount Vernon Hospital and St. Mary's Hospital). This 24-year-old woman presented with menorrhagia after a normal full-term pregnancy. She then developed frontal headaches and bilateral retinal detachments with retinal metastases. Her vision was severely impaired and she lost weight. Diagnostic curettage established a diagnosis of choriocarcinoma, at which time metastases became apparent on the chest *x*-ray film (Fig. 3). The Hogben test was negative throughout the illness, and the gonadotrophin

assay, though raised, never reached the levels usually associated with chorionic tumours. Hysterectomy revealed a rounded 7-cm. choriocarcinoma in the uterus. Radiotherapy was given to the eyes, and cytotoxic therapy was started subsequently. Though the chest *x*-ray film was clear after six weeks of cytotoxic therapy, hormonal remission was achieved only after five months. There was a progressive improvement in visual acuity, and at the completion of therapy this was assessed at approximately 6/12 in both eyes with small residual field defects.

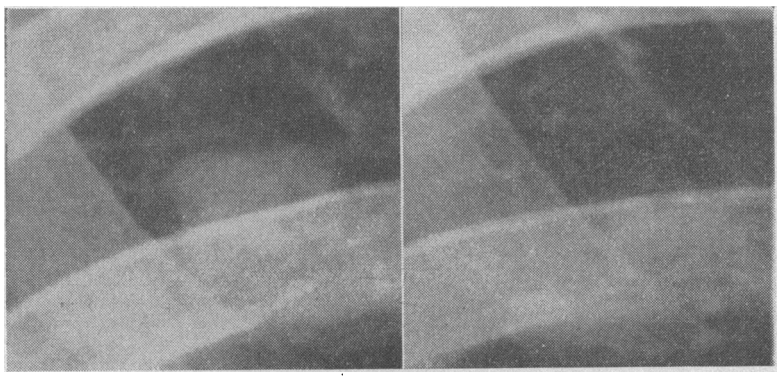


FIG. 3.—Case 3. Left: Part of chest *x*-ray film taken on June 17, 1959, showing pulmonary metastasis. Right: *x*-ray film of same part of chest taken on August 8.

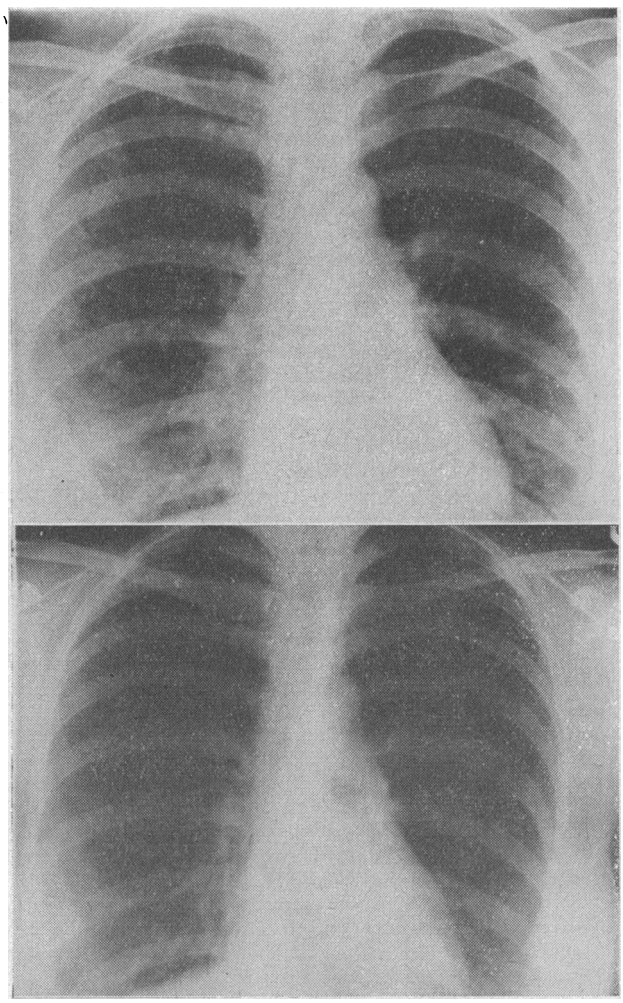


FIG. 4.—Case 4. Top: Chest *x*-ray film taken on July 30, 1959, showing multiple small metastases in both lung fields. Bottom: Chest *x*-ray film taken on September 10, showing radiological clearing after six weeks' treatment.

Case 4 (Paddington General Hospital).—This 24-year-old woman presented with menorrhagia after a normal full-term pregnancy. Diagnosis was made on examination of curettings, and at hysterectomy a 5-cm. diameter haemorrhagic tumour was found in the uterine wall. Pulmonary metastases appeared, but these resolved within six weeks of the start of therapy (Fig. 4). The fall in the gonadotrophin assay was erratic, and after five months' treatment chlorambucil was substituted for 6-mercaptopurine. Normal gonadotrophin levels were attained only after a total of eight months' treatment (Fig. 5). A tendency to prolonged bone-marrow depression contributed to the slow progress in this case. She was in complete remission at the time of reporting.

Case 5 (Luton and Dunstable Hospital).—This 23-year-old woman developed vaginal bleeding five weeks after a normal pregnancy. Examination two months later revealed a mass in the right fornix, and chest *x*-ray examination showed numerous metastases. Examination of uterine curettings confirmed the presence of choriocarcinoma. Methotrexate was started in three-day courses of 15 mg. a day. At first the metastases on the chest *x*-ray film appeared more numerous, and a vaginal metastasis developed. Treatment with only three courses of methotrexate in full dosage was followed by a remarkably rapid disappearance of the mass in the uterus and of the vaginal and pulmonary metastases (Fig. 6). She remained in complete remission at the time of reporting.

Case 6 (St. Mary's Hospital).—This 31-year-old coloured woman had a molar pregnancy in 1954, and hysterectomy was performed in Jamaica. Microscopical examination of the tumour showed areas of active infiltration suggestive of choriocarcinoma. After the operation she developed weakness of the legs and urinary incontinence, suggesting a metastasis involving the cauda equina. Radiotherapy was given to the lower back. Late in 1958 she began to feel ill and to lose weight, and a chest *x*-ray examination in Novem-

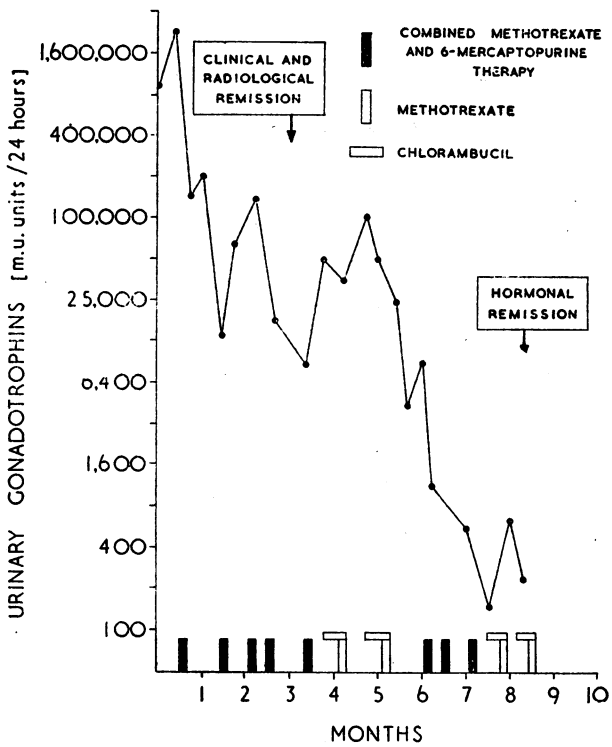


FIG. 5.—Case 4. Urinary gonadotrophin excretion.

ber, 1959, revealed a large well-defined shadow in the left lung field. On presentation for treatment she was severely anaemic and had a staphylococcal pneumonia in addition to a long-standing urinary infection. Methotrexate and 6-mercaptopurine were given under antibiotic cover, and severe intestinal bleeding followed. She became confused, and after the second course of treatment developed focal seizures. The third course of treatment consisted of a three-day course of intrathecal methotrexate, and she had no further fits until after the fourth course of treatment. Heavy sedation was then necessary to control the fits, and this coincided with the hepatic dysfunction which followed cytotoxic therapy. She died in coma 10 days after the end of the fourth treatment. Necropsy was performed by Dr. K. Porter, and revealed a necrotic mass in the left lung and two small necrotic cerebral metastases. On histological examination all recognizable tumour cells showed pyknosis and other degenerative changes. There was extensive renal infection and histological evidence of focal hepato-cellular damage.

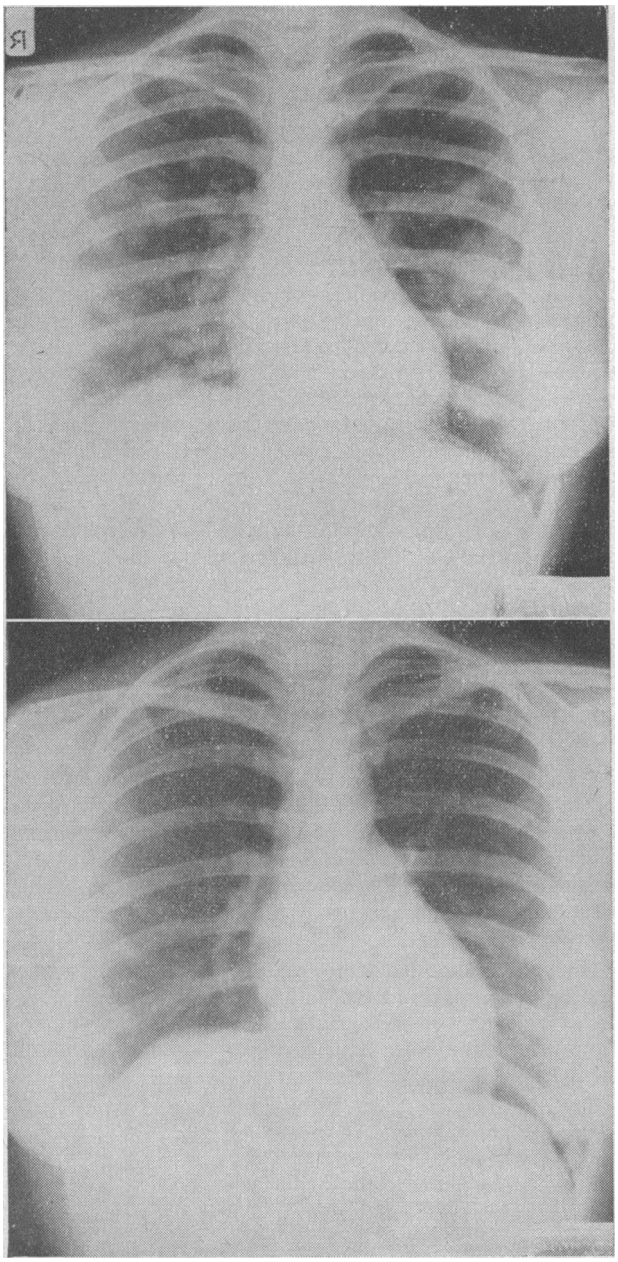


FIG. 6.—Case 5. Top: Chest x-ray film taken on May 17, 1959, showing multiple metastases in both lung fields. Bottom: Chest x-ray film taken on November 10, showing complete radiological resolution.

Side-effects of Treatment

Serious toxic effects are invariably encountered in the systemic administration of large doses of antimetabolite substances, and deaths have been attributed to intestinal, hepatic, and bone-marrow damage (Hertz *et al.*, 1958). The use of a combination of antimetabolite drugs in massive dosage might be expected to cause more severe toxic damage. Though side-effects in the present group were severe, they do not appear to have been appreciably worse than those encountered in the use of folic-acid antagonists alone. The one death in the present series could be partially attributed to the drugs aggravating a pre-existing renal infection and to impaired detoxication of anti-epileptic drugs.

The common side-effects were stomatitis, proctitis, nausea, vomiting, occasional diarrhoea, intestinal bleeding, jaundice, paronychial infections, blotchiness of the skin, pigmentation, diffuse alopecia, anaemia, leucopenia, thrombocytopenia, and proteinuria. Side-effects became apparent between the fourth and eighth days after the start of each course of treatment. They were maximal between the seventh and fourteenth days, and recovery from the acute effects was complete between the tenth and twentieth days.

Stomatitis proved to be the most trying symptom. Jaundice was transient, but gross temporary derangement of liver function was revealed by "bromsulphalein" excretion tests immediately after a course of treatment. Liver-function tests on completion of therapy have been normal. Proteinuria has been mild and usually occurred only after the initial courses of treatment. Detailed studies of renal function have not been performed, but blood-urea levels have remained normal throughout, except in Case 6, in which there was a long-standing urinary infection.

Haemoglobin levels during treatment were usually in the range of 7–11 g./100 ml., and progressive falls did not commonly occur. In Case 4 bone-marrow depression, especially with respect to the platelets, tended to be more severe and to persist longer after each course of treatment than in the other cases, and this has led to prolongation of treatment.

Alopecia progressed steadily throughout the first four to five months of treatment, though hair growth recurred before each course, and towards the end of treatment this appeared to proceed despite further cytotoxic therapy. After completion of therapy hair growth and texture returned to normal.

Control of Side-effects

A normal diet was given throughout, except when prohibited by stomatitis. No attempt was made to restrict or augment the folic-acid content of the diet. On some occasions parenteral fluid therapy was necessary.

Stomatitis was partially alleviated by a variety of local measures, but when it was severe intramuscular pethidine provided the only satisfactory relief. Latterly, a very weak solution of folinic acid was applied to the buccal mucosa during treatment, and this appeared to diminish the severity of the stomatitis. It is not yet certain whether such applications have an adverse effect on the course of treatment, but this seems improbable.

Specific therapy for bone-marrow depression was necessary on only two occasions, and consisted of

transfusions of fresh blood and folinic acid in doses of up to 18 mg. a day.

The risk of irreversible bone-marrow damage was always present during this form of treatment. Because of this risk, bone-marrow was aspirated from four of the patients and was cooled and stored at −78° C. by methods similar in principle to those described elsewhere (see, for example, Pegg and Trotman, 1959). The occasion to return stored marrow has not so far arisen in the patients under review, but it would seem to be unjustifiable not to make use of this potential safety factor in the event of a failure to respond to folinic acid. The fact that severe marrow depression after cytotoxic therapy may recover without marrow transfusions is illustrated by the events in Case 1 (Fig. 2); a similar sequence occurred in Case 5. Bone-marrow depression was not evident in Case 6 at the time of death.

The provision of wigs was of value in reducing mental depression and resistance to further therapy on account of alopecia.

General Discussion

The remissions from widespread malignant choriocarcinoma which have been achieved in five of these six cases and in some of the much larger group reported by Hertz *et al.* (1958) have probably been more profound than those seen in other forms of malignant disease treated by chemotherapeutic methods. While it is too early to regard these cases as cured, the possibility that this may have occurred in at least some instances cannot be dismissed. Moreover, it should be possible to detect hormonal evidence of recurrence of such tumours before there is any clinical or radiological evidence of their recurrence. The fact that two patients in this series received large amounts of folinic acid at the end of their treatment without evidence of relapse supports the view that any remaining tumour cells were not capable of active metabolism and division at that time. The administration of folinic acid after completion of therapy as a test for the presence of viable tumour cells suggests itself, but further experience will be required before this can be safely, or reliably, established.

The treatment of trophoblastic tumours with these agents may have some bearing on the treatment of other forms of malignant disease, and a quantitative guide to therapy such as the gonadotrophin assay emphasizes the insensitivity of clinical and radiological methods as such a guide. It is notable that though malignant trophoblastic tumours appear to be more sensitive to certain cytotoxic agents than many other tumours, the amount and duration of therapy necessary to achieve full remission is considerably greater than that usually employed in the chemotherapy of malignant disease.

It will be possible to define the place of surgical intervention in the treatment of choriocarcinoma only after much further experience has been gained with cytotoxic methods. Clearly, hysterectomy may have to be performed either to establish the diagnosis or to stop haemorrhage. Even when neither of these reasons applies it may be advisable to remove the uterus when it is the site of a large tumour, because the risk of haemorrhage seems to be greater when a large tumour is undergoing necrosis. Similarly, there may be a case for the removal of a large solitary pulmonary metastasis, especially if situated peripherally and if there is haemorrhage. However, Case 5 demonstrates that these complications are by no means inevitable even with large metastases. It may be significant, also, that the two patients who did not have hysterectomy and oophorectomy responded most readily to cytotoxic treatment. On the present evidence it seems that hysterectomy and oophorectomy should not be performed without adequate reason, even though the spontaneous disappearance of metastases has been reported on rare occasions after surgical removal of the primary tumour.

It is evident from the work of Hertz *et al.* (1958), Li (1959), and Douglas (1959) that complete hormonal remissions have been obtained in about 25% of patients with malignant trophoblastic tumours treated with folic-acid antagonists alone. In other cases initial sensitivity to folic-acid antagonists has been followed by partial or complete resistance. Where other forms of chemotherapy have been used subsequent to the development of resistance to folic-acid antagonists, continued failure to respond has suggested a crossover in tumour resistance to other forms of chemotherapy (Hertz, 1959). In the present series drug resistance was not encountered in the six patients treated. One of our patients (Case 4) may have developed partial resistance to methotrexate and 6-mercaptopurine, but a full remission followed treatment with methotrexate and chlorambucil used alternately with methotrexate and 6-mercaptopurine (Fig. 5).

Owing to the small size of the present series it is not possible to draw definite conclusions concerning the relative merits of the use of anti-folic-acid substances on the one hand and their administration concurrently with other cytotoxic agents on the other. It seems clear, however, that the hazards of combined cytotoxic therapy under carefully controlled conditions, though substantial, are not significantly greater than those of anti-folic-acid therapy alone. Furthermore, the present evidence suggests that the concurrent administration of a second cytotoxic agent may substantially reduce the incidence of drug resistance. Much further study on the effectiveness of alternative drug combinations is required.

The fact that choriocarcinoma is now amenable to cytotoxic therapy inevitably imposes an obligation to establish the diagnosis at the earliest moment. Moreover, though these tumours are rare, their unusual features give them an important position in the study of the chemotherapy of cancer.

Summary

The treatment of six cases of widely metastasized choriocarcinoma with combinations of methotrexate, 6-mercaptopurine, and chlorambucil is reported. The complications and control of this treatment are considered.

One patient died during treatment, and at necropsy the tumour appeared to be totally necrotic. Five patients have achieved complete clinical, radiological, and hormonal remission from their choriocarcinomata. One of these has a persistent pulmonary hypertension.

The duration of these remissions ranged from 2 to 19 months at the time of reporting.

This study was undertaken with the support of the Edgar-Gentilli Scholarship. We wish to thank Professor T. N. A. Jeffcoate, chairman of the Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists, for his generous help. We are indebted to Dr. Margaret I. Stern, Miss Joan Bonfield, and other members of the staff of the Endocrine Unit, Chelsea Hospital for Women, working

under the direction of Dr. Ian F. Sommerville, for their help with the gonadotrophin assays. We also thank Dr. W. D. W. Brooks, Mr. G. C. Brentnall, Dr. H. E. Edwards, Miss A. M. Fleming, Professor W. S. Peart, Professor Sir George W. Pickering, Mr. I. Spiro, and Dr. P. Strickland for permission to study their patients and publish case reports. We also thank the registrars, house staff, and nursing staff whose co-operation made this study possible.

REFERENCES

Bagshawe, K. D., and Brooks, W. D. W. (1959). *Lancet*, **1**, 653.
Douglas, G. W. (1959). *Ann. N.Y. Acad. Sci.*, **80**, 277.
Hertz, R., and Tullner, W. W. (1949). *Endocrinology*, **44**, 278.
—— —— —— —— —— (1959). *Ann. N.Y. Acad. Sci.*, **80**, 262.
—— Bergenstal, D. M., Lipsett, M. B., Price, E. B., and Hilbish, T. F. (1958). *J. Amer. med. Ass.*, **168**, 845.
Klinefelter, H. F., Albright, F., and Griswold, G. C. (1943). *J. clin. Endocr.*, **3**, 529.
Li, M. C. (1959). *Ann. N.Y. Acad. Sci.*, **80**, 280.
—— Hertz, R., and Spencer, D. B. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **93**, 361.
Loraine, J. A. (1950). *J. Endocr.*, **6**, 319.
—— and Brown, J. B. (1954). *Acta endocr. (Kbh.)*, **17**, 250.
Nelson, M. M., and Evans, H. M. (1949). *J. Nutr.*, **38**, 11.
Pegg, D. E., and Trotman, R. E. (1959). *J. clin. Path.*, **12**, 477.
Skipper, H. E., Thomson, J. R., and Bell, M. (1954). *Cancer Res.*, **14**, 503.
Watts, R. M., and Adair, F. L. (1943). *Amer. J. Obstet. Gynec.*, **46**, 183.

NUCLEAR SEX AND BODY-BUILD IN SCHIZOPHRENIA

BY

VALERIE COWIE, M.D., D.P.M.
Assistant Director, Medical Research Council Psychiatric Genetics Research Unit, Maudsley Hospital, London

ALEC COPPEN, M.D., D.P.M.
Institute of Psychiatry, Maudsley Hospital, London

AND

PATRICIA NORMAN, B.Sc.*
Research Assistant, Department of Clinical Pathology, King's College Hospital, London

A recent survey on body-build has shown that schizophrenics differ markedly from normal subjects with regard to the biacromial diameter and the androgyny score. Groups of patients of both sexes were found to have a much lower (more female) androgyny score and a smaller biacromial diameter than did groups of normal men and women (Rey and Coppen, 1959). The androgyny score is obtained by the formula :

3 × biacromial diameter (cm.) − 1 × bi-iliac diameter (cm.).

The androgyny score for normal individuals has been shown to have a normal distribution for each sex, with a mean of 90.1 (S.D. 4.7) for men and of 78.9 (S.D. 4.6) for women (Tanner, 1951). The androgyny score enables effective discrimination to be made between the sexes. Out of 409 men and women examined by Tanner (1951) only 12% were misclassified on the basis of the androgyny score.

The biacromial diameter and the androgyny score are closely related to sexual development (Rey and Coppen, 1959). Moreover, it has been found that anatomical males with chromatin-positive cells have smaller biacromial diameters than normal subjects (Raboch, 1957 ; Coppen and Cowie, 1960).

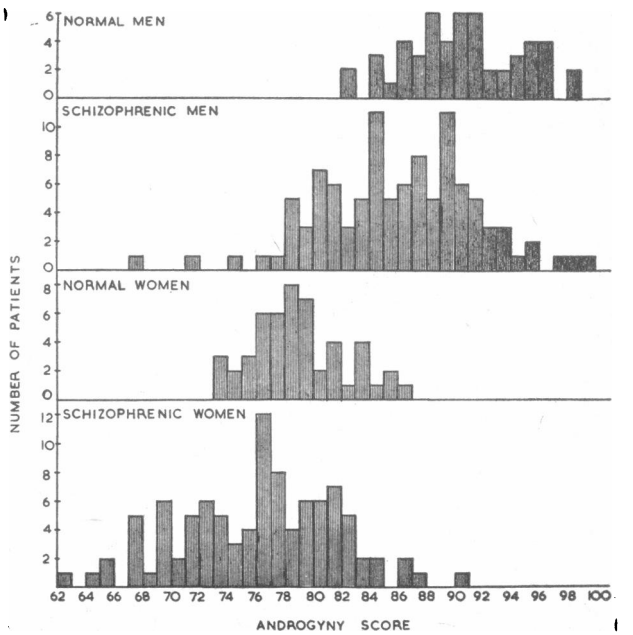
There are grounds for believing that some connexion may exist between anomalies of nuclear sex and mental disorders. Thus Pasqualini *et al.* (1957) described a number of individuals with Klinefelter's syndrome who showed hypokinesis and timidity from an early age. They were usually idle, slept too much, lacked vital interests, and were shy, restrained, and had few friends. They were of low intelligence with a mean I.Q. of 81. In line with this last observation Ferguson-Smith (1958, 1959) found that just over 1% of male patients in a mental deficiency hospital and 1.2% of educationally subnormal male children had chromatin-positive Klinefelter's syndrome. These percentages greatly exceed that of 0.26% reported by Moore (1959) in an unselected group of newborn male infants.

Taking all these facts into consideration, it is not unreasonable to suspect that there may be changes in nuclear sex associated with schizophrenia. However, as many schizophrenics have a normal physique and as the classification of schizophrenia may well include heterogeneous groups of patients, it seems likely that if anomalies of nuclear sex occurred in this condition they would be found in patients with a female type of body-build.

In the present investigation male schizophrenics with an androgyny score characteristic of normal women were selected from a schizophrenic population for the examination of nuclear sex. A similar examination was carried out with a group of female schizophrenics with significantly reduced androgyny scores, as it is known that women with gonadal dysgenesis frequently have anomalies of physique and often lack sex chromatin (Grumbach *et al.*, 1955).

The Investigation

We examined 100 male and 100 female mental hospital patients with a diagnosis of chronic schizophrenia. In every case the biacromial and bi-iliac diameters were measured with a Martin anthropometer. The androgyny scores for patients of both sexes are shown in the Chart. The mean androgyny scores for both the male and the female



Distribution of androgyny score in schizophrenic patients and normal subjects.

*In receipt of a grant from the Medical Research Council.